

Melanocytic Nevus

Pigmented nevus (mole)

Pathogenesis • Morphology • Diagnostic interpretation

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Learning objectives

- Explain why nevi are benign melanocytic neoplasms despite oncogenic pathway activation.
- Recognize junctional, compound, and intradermal growth patterns.
- Describe maturation with depth and its diagnostic significance.
- Compare representative nevus variants and distinguish risk markers from ordinary nevi.

The essential definition of a melanocytic nevus

- A common benign neoplasm of melanocytic lineage.
- Usually associated with acquired activating mutations in RAS-pathway components.
- Encompasses clinically and histologically diverse lesions rather than one uniform appearance.
- The ordinary acquired nevus is the most frequent form.

Pigmentation is not synonymous with a nevus

Pigmented skin lesion

- Describes color, not its cause.
- May reflect pigment within keratinocytes.
- Requires an architectural diagnosis.

Melanocytic nevus

- Benign melanocytic neoplasm.
- Nevus-cell aggregates or nests.
- May show junctional and/or dermal components.

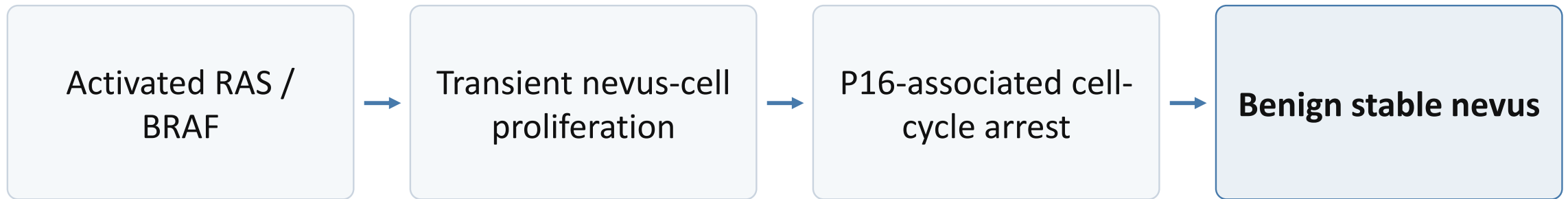
Why nevi are considered neoplastic

- Many harbor acquired mutations that constitutively stimulate RAS or BRAF.
- Clonal signaling activation provides a proliferative stimulus.
- Their benignity reflects subsequent growth restraint, not absence of oncogenic signaling.
- Morphology remains essential; A mutation alone does not establish melanoma.

Ordinary acquired nevi are ubiquitous

- The usual acquired melanocytic nevus is extremely common.
- Most individuals have at least a few moles.
- Routine nevi are generally small and clinically regular.
- Biologic diversity becomes important when assessing an atypical lesion.

The core biologic paradox



An oncogenic driver may initiate a lesion without producing sustained malignant growth.

RAS-pathway activation initiates nevus formation

- The RAS signaling pathway is a frequent molecular target in acquired nevi.
- Activating mutations sustain signaling in affected melanocytes.
- The signal initially drives a limited proliferative phase.
- A built-in antiproliferative response subsequently constrains lesion growth.

BRAF lies immediately downstream of RAS



The source identifies BRAF as a serine/threonine kinase immediately downstream of RAS.

Activated signaling: Driver versus phenotype

Genetic event

- Acquired activating mutation.
- RAS or BRAF can signal constitutively.
- Provides proliferative drive.

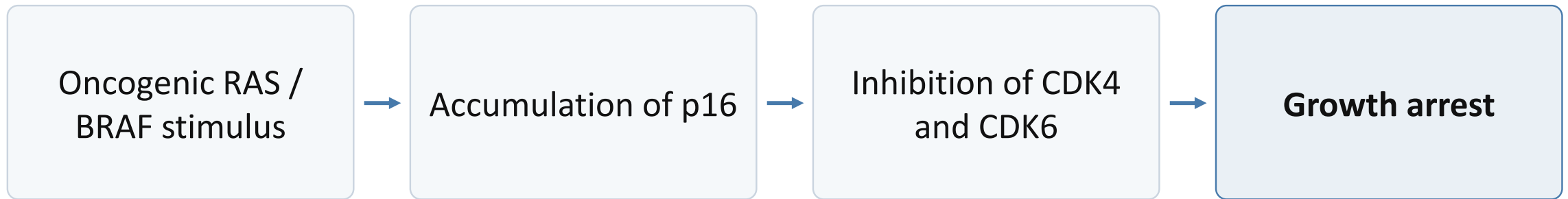
Observed phenotype

- Growth does not continue indefinitely.
- Most lesions remain benign.
- Growth arrest changes the biological outcome.

Oncogene-induced senescence

- Activated RAS or BRAF stimulates a limited proliferative interval.
- The same stimulus is followed by a relatively permanent growth arrest.
- This is oncogene-induced senescence.
- The response helps explain why ordinary nevi rarely become melanoma.

P16 constrains the cell cycle



The source specifies p16 as an inhibitor of cyclin-dependent kinases, including CDK4 and CDK6.

The role of p16

- P16 is a cell-cycle inhibitor that contributes to nevus-cell growth arrest.
- Its accumulation follows ectopic or acquired activation of RAS/BRAF signaling.
- By inhibiting CDK4/CDK6, p16 counteracts proliferative drive.
- This is a protective barrier, not an assurance that progression is impossible.

Why most nevi do not progress

Initiating signal

- Mutations promote proliferation.
- Constitutive RAS/BRAF activity.
- Can occur in benign nevi.

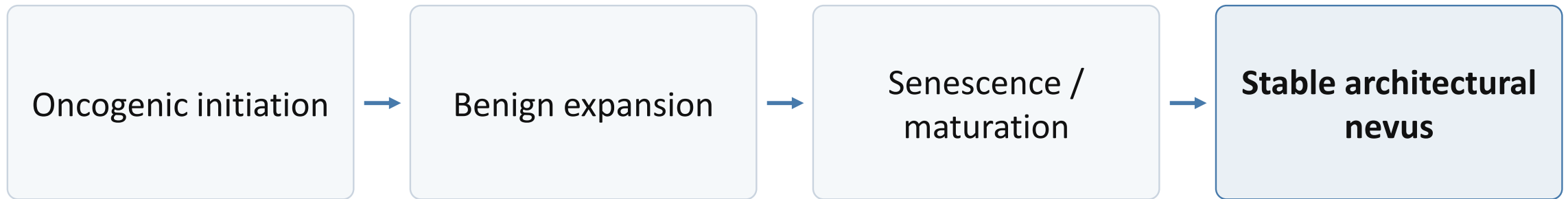
Progression restraint

- P16 rises.
- Senescence interrupts cell cycling.
- Further alteration is needed to escape restraint.

Melanoma disrupts this protective restraint

- Senescence disruption in melanoma and some precursor lesions.
- Loss of the growth barrier permits continued expansion.
- A shared initiating driver does not imply equivalent biological behavior.
- Interpret mutation findings in their morphological and clinical context.

Molecular-to-morphologic integration



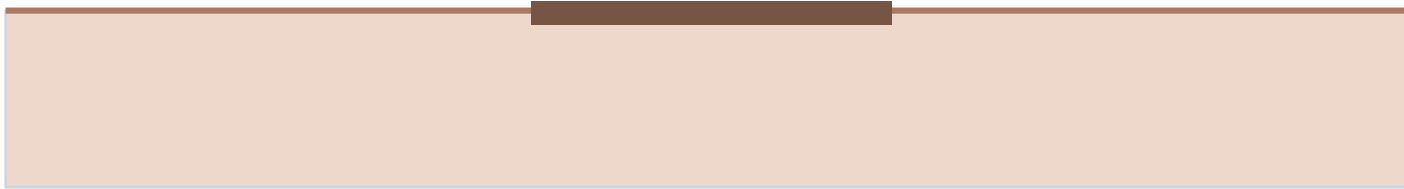
The model links molecular arrest to the observed maturation of nevus cells with depth.

What does a typical acquired nevus look like?

- Usually tan to brown and relatively uniformly pigmented.
- Typically small, generally less than 6 mm across.
- Well-defined and rounded in outline.
- May be a flat macule or elevated papule.

Flat nevus: A macular phenotype

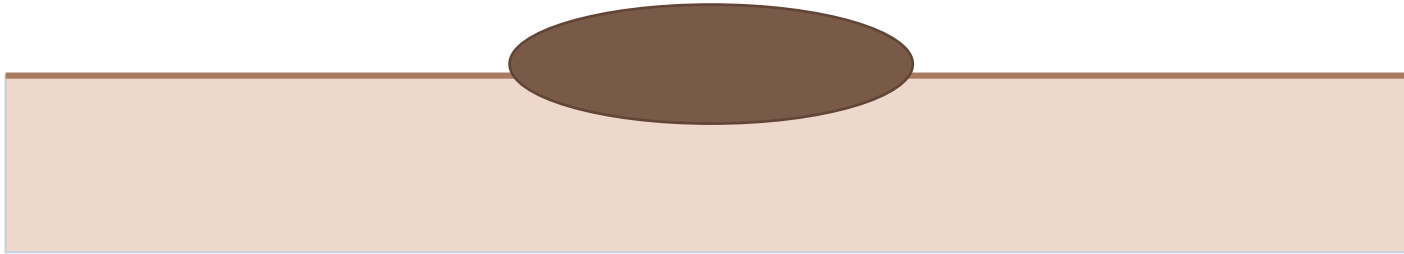
- Relatively flat surface.



- Uniform brown pigmentation.
- Well-defined rounded border.

Schematic surface profile — not a clinical photograph

Elevated nevus: A papular phenotype



- Raised surface contour.
- May retain pigment uniformity.
- Common in later morphologic stages.

Schematic surface profile — not a clinical photograph

Symmetry and pigment uniformity

Ordinary acquired nevus

- Often symmetric shape.
- Relatively uniform pigment.
- Smooth, circumscribed margin.

Diagnostic interpretation

- Consistent with a benign pattern.
- Does not independently prove benignity.
- Must be considered with histologic architecture.

Size and border in conventional nevi

- Ordinary acquired lesions are usually less than 6 mm in diameter.
- A well-demarcated, rounded margin is typical.
- These are descriptive tendencies rather than absolute diagnostic cutoffs.
- Atypical features should trigger broader morphologic evaluation.

Pregnancy-related prominence

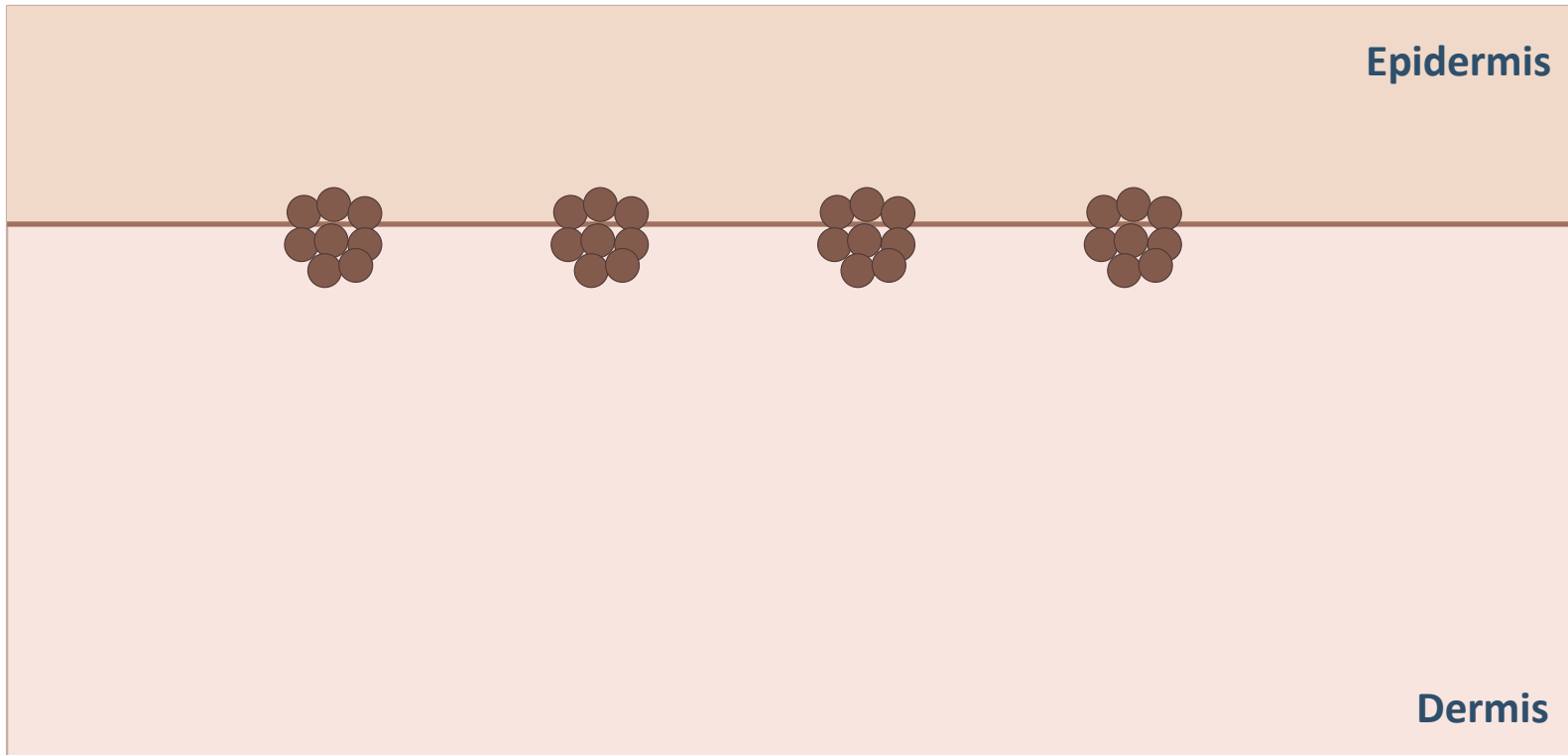
- Nevi may become more prominent during pregnancy.
- This observation supports a degree of hormonal sensitivity.
- Prominence alone does not establish malignant transformation.
- Morphological context is more informative than isolated change.

A proposed morphologic sequence



This is a typical conceptual progression, not a mandatory timeline for every lesion.

Junctional nevus: The earliest common pattern



- Nests cluster at junction.
- Dermis lacks a nevus-cell component.
- Often clinically flat.

Schematic: Round nests at the dermoepidermal junction

Why junctional nevi are called “junctional”

- Nevus cells collect along the epidermal–dermal interface.
- Rounded nests are seen near tips of rete ridges.
- This distribution defines the architectural compartment.
- Recognition begins at low magnification with the lesion location.

Cytology of ordinary nevus cells

- Nuclei tend to be uniform and rounded.
- Nucleoli are generally inconspicuous.
- Little or no mitotic activity is expected.
- The orderly pattern complements the architectural diagnosis.

Architecture and cytology are complementary

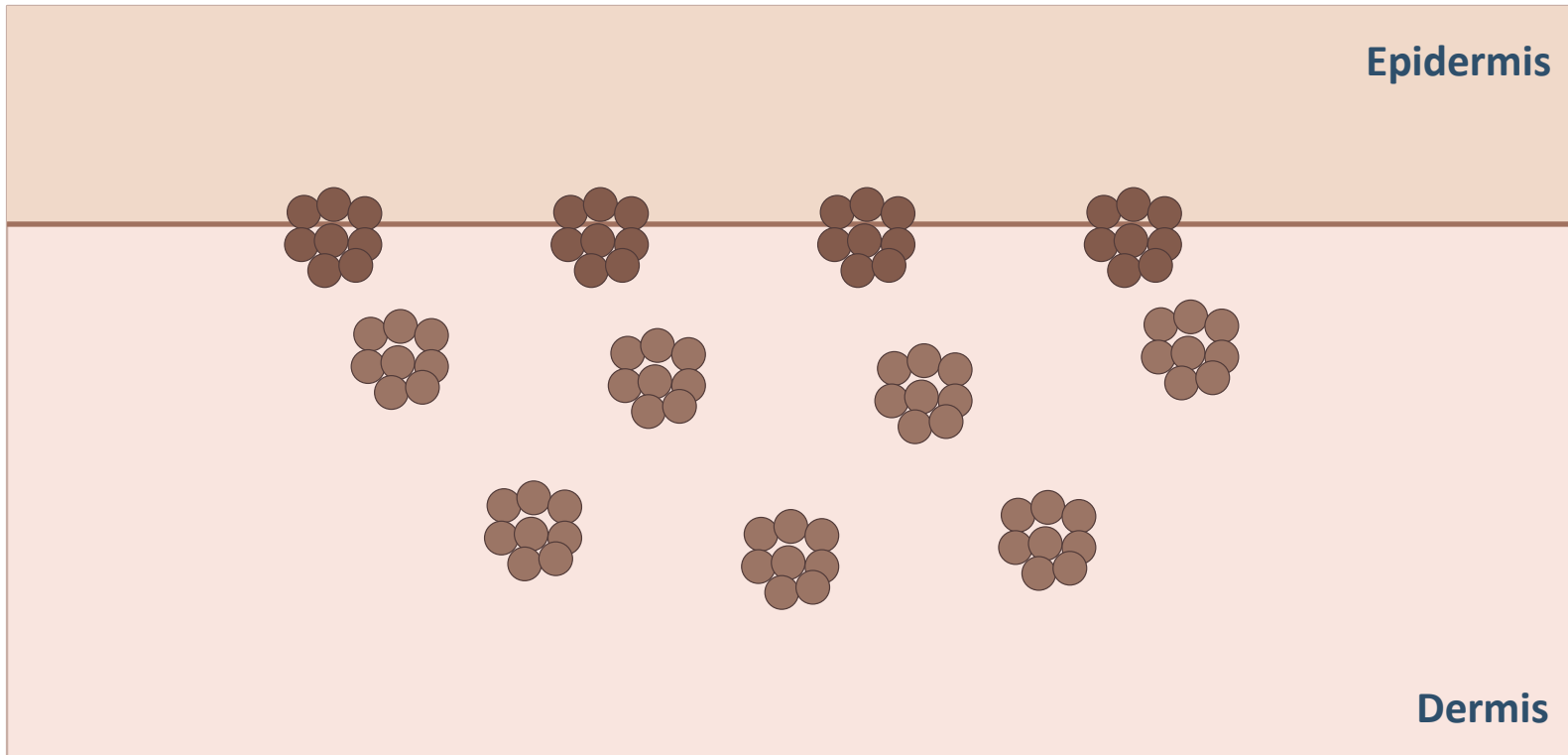
Architecture

- Junctional nests.
- Symmetric lesion organization.
- Subsequent dermal components in compound nevi.

Cytology

- Uniform rounded nuclei.
- Subtle nucleoli.
- Minimal mitotic activity.

Compound nevus: Junctional plus dermal elements



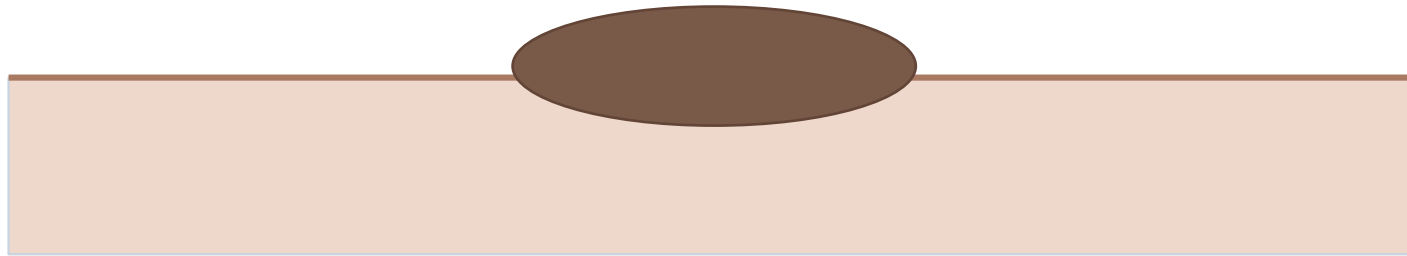
- Persistent junctional nests.
- Nests and cords in dermis.
- Often dome-shaped and raised.

Schematic: Junctional nests coexist with dermal growth

How a compound nevus forms

- Nevus cells extend from the junction into the underlying dermis.
- Dermal cells aggregate as nests and cords.
- Some junctional nests remain visible.
- The resulting lesion has two recognizable compartments.

Why compound nevi tend to be elevated



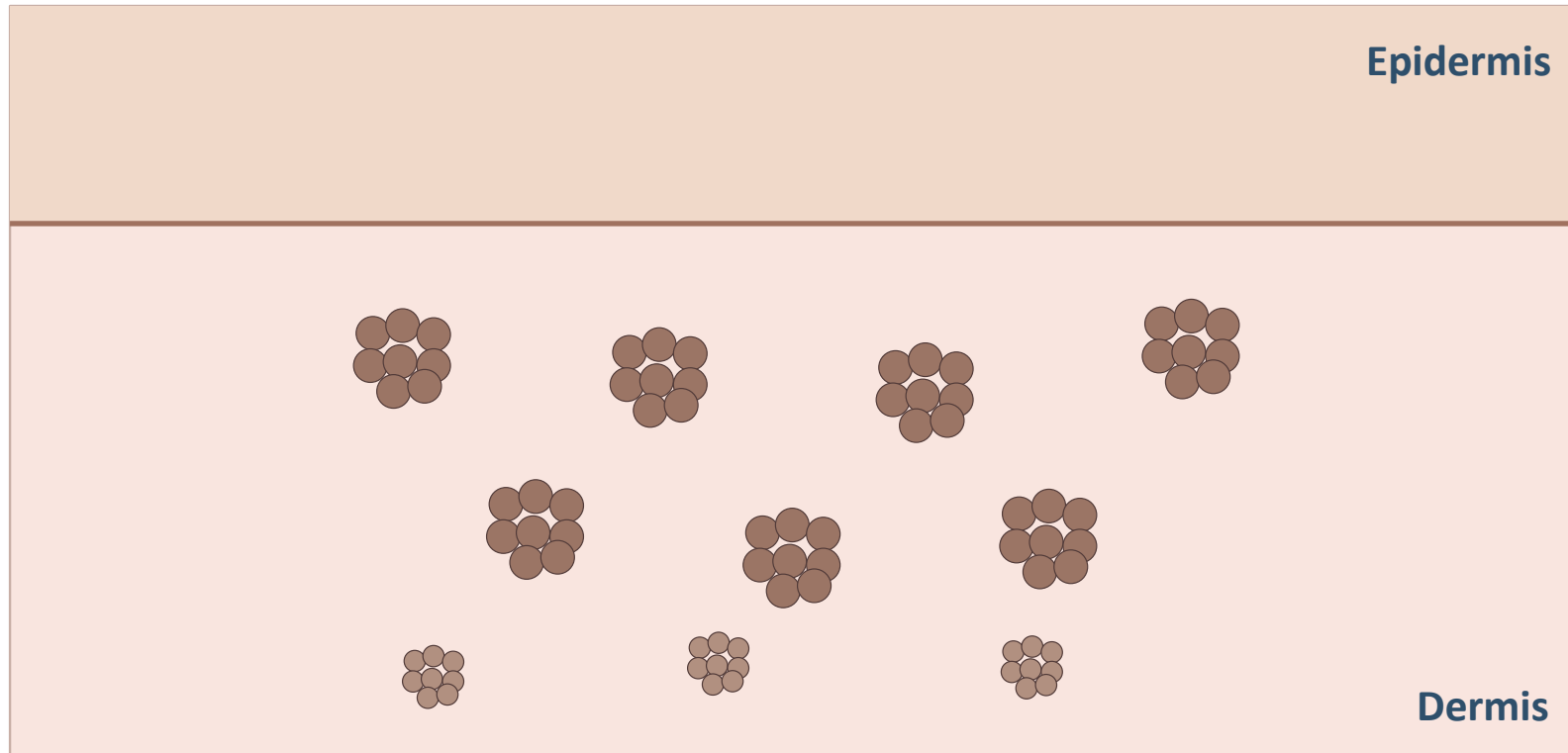
- Dermal cell volume adds bulk.
- Surface may become dome-shaped.
- Symmetry remains a useful clue.

Schematic surface profile — not a clinical photograph

Compound nevus: An architectural checklist

- Identify intraepidermal or junctional nevus-cell nests.
- Identify dermal nests or cords beneath those nests.
- Examine change in cell size and pigmentation with depth.
- Assess overall organization together with bland cytology.

Intradermal nevus: Epidermal nests have disappeared



- Nevus cells restricted to dermis.
- No remaining epidermal nests.
- Typically more elevated.

Schematic: Nevus cells entirely below the junction

Understanding the intradermal stage

- Older lesions may lose their junctional nests entirely.
- Residual nevus cells are then confined to the dermis.
- These lesions are termed pure intradermal nevi.
- Like compound nevi, they are commonly raised.

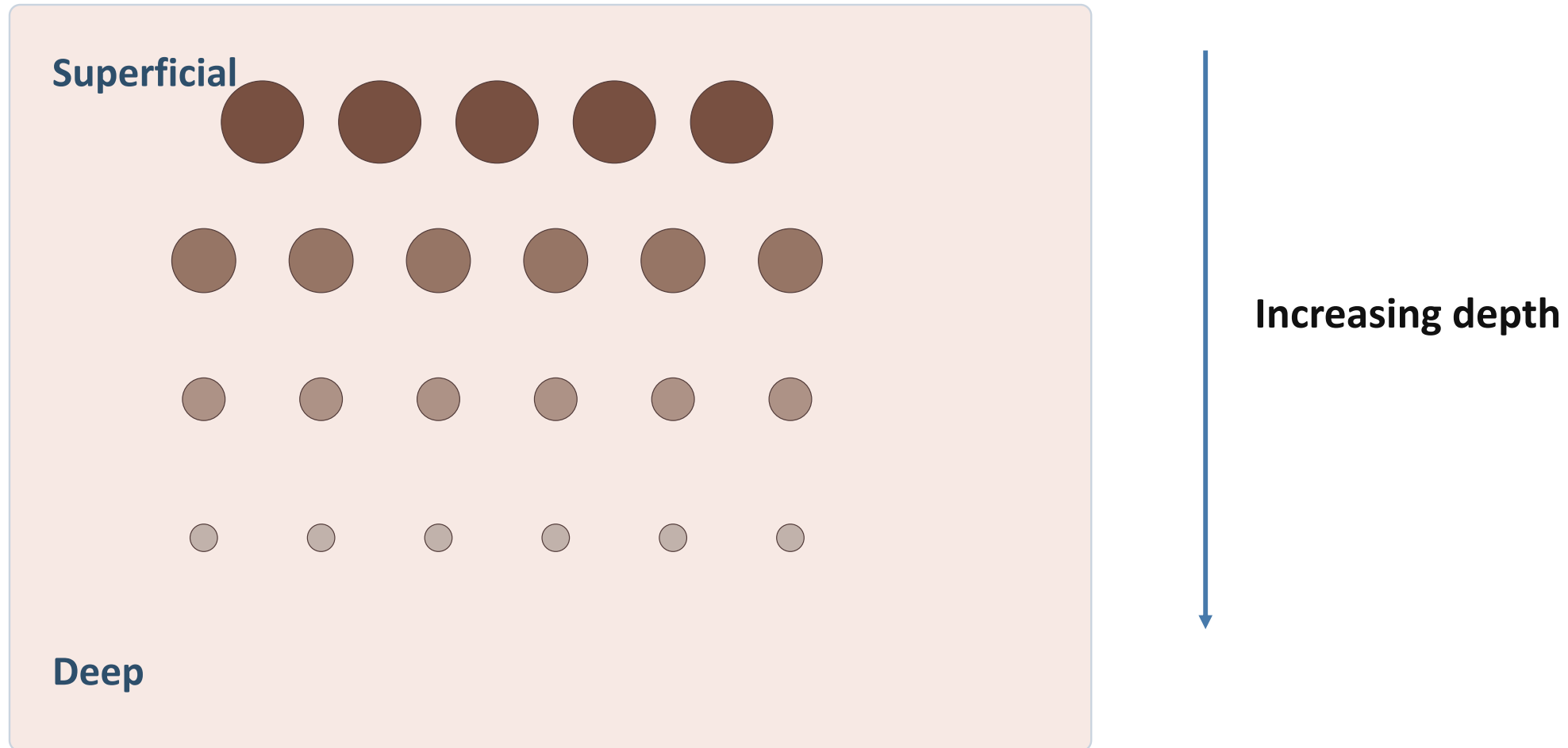
Three principal acquired nevus architectures

Type	Junctional nests	Dermal nevus cells	Clinical contour
Junctional	Present	Absent	Often relatively flat
Compound	Present	Present	Frequently elevated
Intradermal	Absent	Present	Frequently elevated

Maturation with depth: A benign pattern

- Superficial nevus cells tend to be larger and more pigmented.
- Deeper nevus cells progressively decrease in size and pigment.
- Growth shifts from nests toward cords and individual cells.
- This patterned transition is characteristic of ordinary nevi.

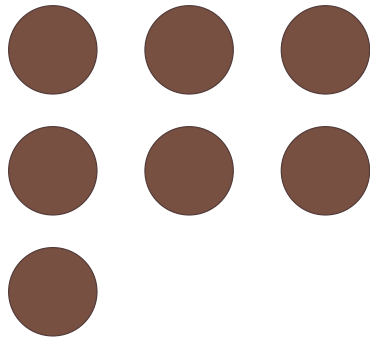
Maturation: Cell size decreases with depth



Progressive reduction in cell size supports benign nevus maturation.

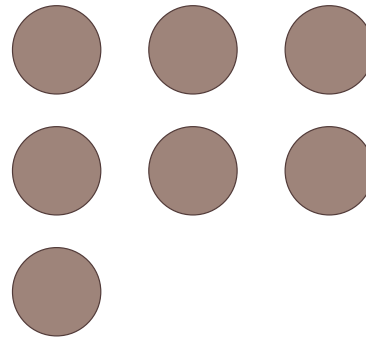
Maturation: Pigment production diminishes

Superficial



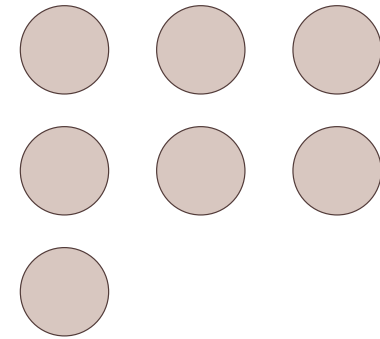
More melanin

Intermediate



Less melanin

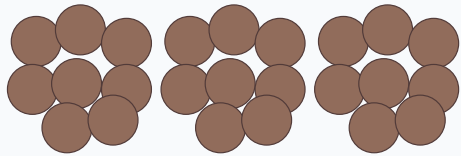
Deep



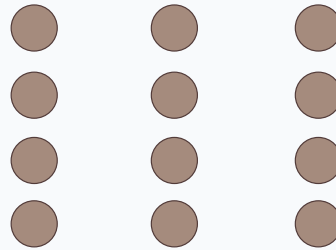
Little or no pigment

Maturation: Nesting shifts to cords and single cells

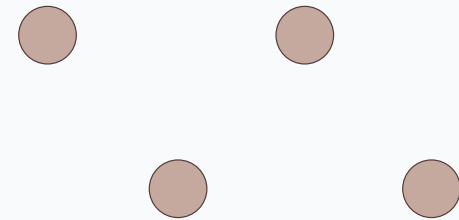
Superficial nests



Deeper cords



Deep single cells



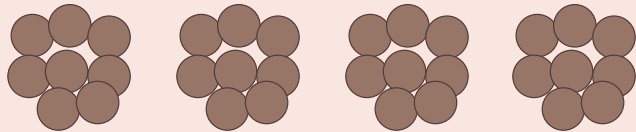
Architecture changes with depth; This is a conceptual drawing, not H&E.

Neurotization at the deepest aspect

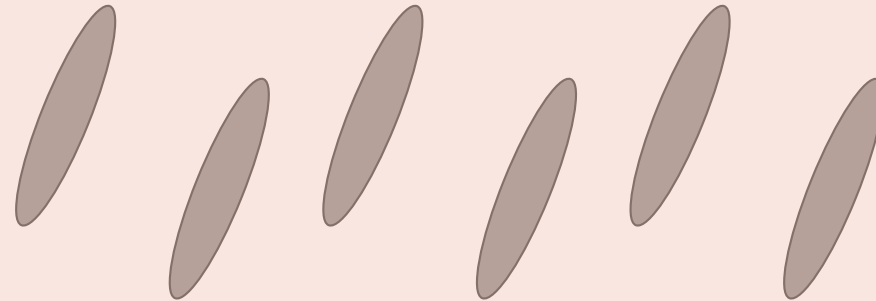
- Deep nevus cells may become fusiform or spindle-shaped.
- They may be arranged in fascicles resembling neural tissue.
- Robbins refers to this morphological pattern as neurotization.
- It represents deep maturation rather than a separate neural neoplasm.

Neurotization: A schematic of deep spindle-cell change

Superficial rounded nevus cells



Deep spindle-shaped fascicles

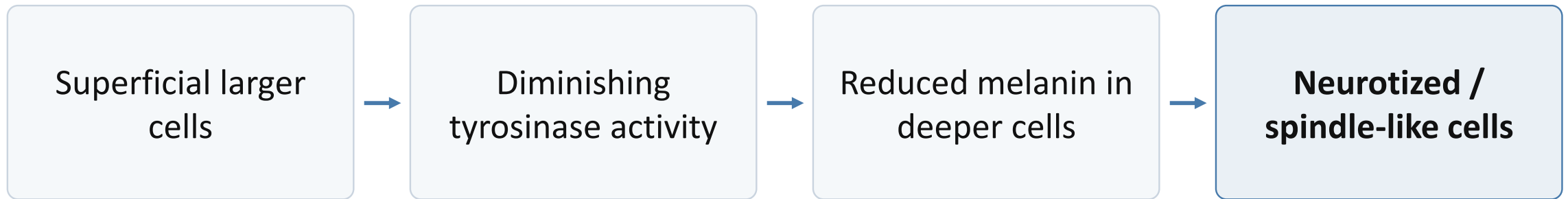


Schematic cellular transformation; Proportions are illustrative

Tyrosinase activity parallels nevus-cell maturation

- Tyrosinase activity decreases in progressively deeper nevus cells.
- Deep nonpigmented cells often appear nerve-like.
- Decreased enzyme activity correlates with reduced pigment formation.
- Biochemical and microscopic maturation therefore align.

Pigment and cell form: Linked changes



A correlation, not proof that enzyme loss causes neurotization.

Benign maturation versus failure of maturation

Typical benign nevus

- Smaller deep cells.
- Reduced deep pigmentation.
- Cords / single cells / neurotization.
- Little or no mitotic activity.

Concerning interpretation

- Absent orderly maturation is a warning clue.
- Evaluate architecture and cytology together.
- Do not diagnose malignancy from one feature.
- Escalate to full clinicopathologic assessment.

What histology explains about clinical evolution

- Junctional nests tend to correspond to flatter lesions.
- Addition of dermal cells increases lesion bulk.
- Loss of junctional nests can leave an elevated intradermal lesion.
- Maturation may occur as the lesion ages.

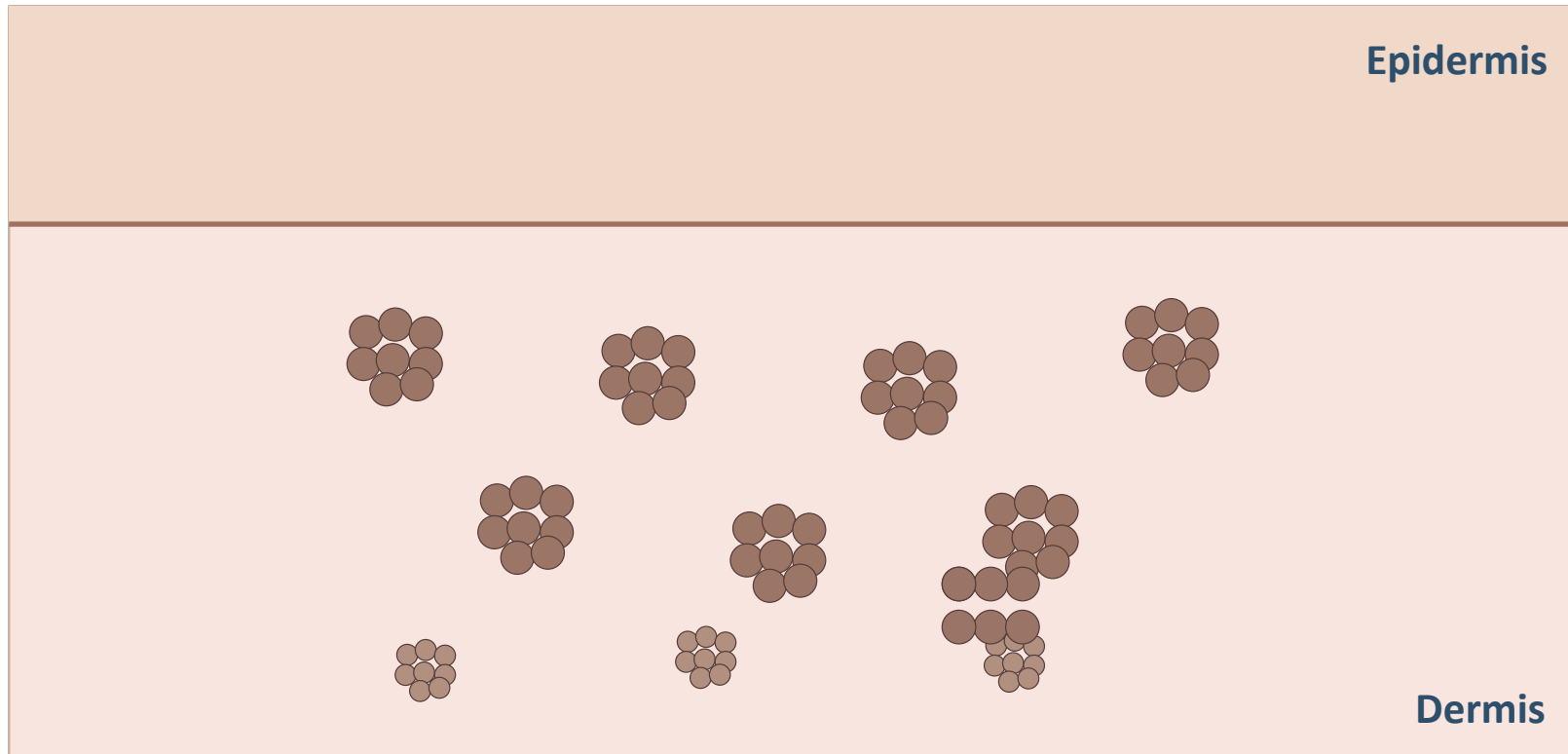
The term “nevus” covers biologic diversity

- Acquired nevi are only one part of the category.
- Congenital, blue, Spitz, and halo nevi show distinctive patterns.
- The same clinical color may reflect different architectural forms.
- Subtype recognition prevents misclassification.

Congenital melanocytic nevus

- Present at birth rather than newly acquired later.
- Histologically may extend deeply around skin adnexa and vessels.
- Lesional cells may involve deep dermis or subcutis.
- Large congenital forms have increased melanoma risk.

Congenital nevus: Deeper anatomic involvement



- Around adnexa
- Around neurovascular bundles
- Along vessel walls
- May reach subcutis

Schematic anatomy; No specimen image used

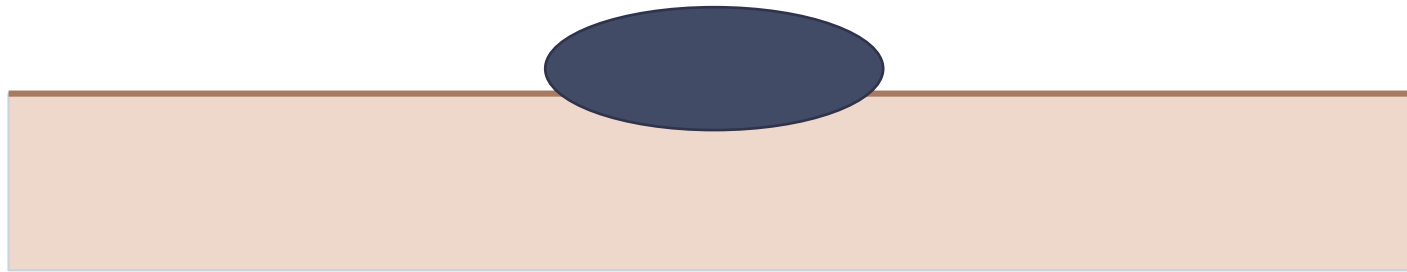
Congenital nevus: Clinical risk is size-dependent

- Large congenital nevi as carrying increased melanoma risk.
- The source does not supply an absolute risk percentage for this entry.
- Ordinary acquired nevi should not be assigned the same risk profile.
- Architecture and clinical history help distinguish congenital from acquired forms.

Blue nevus: Why the lesion appears striking

- The clinical lesion may be a black-blue nodule.
- Dermal nevus cells can be strongly pigmented and dendritic.
- Histology shows nonnested infiltration within the dermis.
- Associated fibrosis is common in the source description.

Blue nevus: A clinical mimic of melanoma



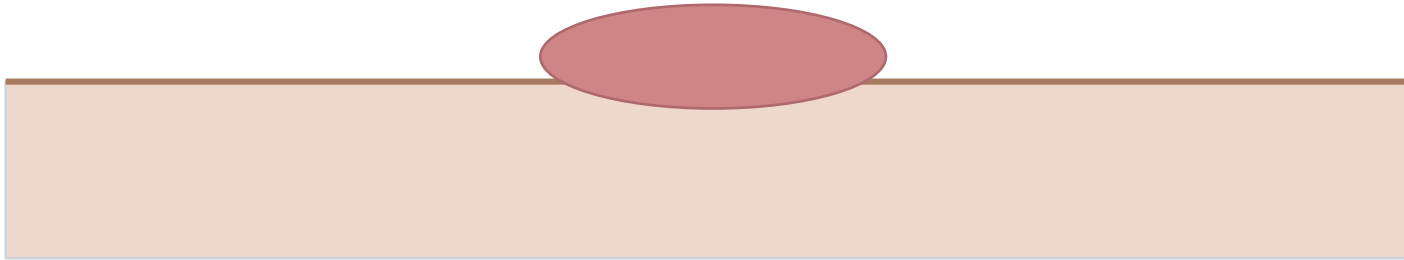
- Blue-black nodule.
- Deeply pigmented dermal cells.
- May appear alarming clinically.

Schematic surface profile — not a clinical photograph

Spitz nevus: Distinctive cellular morphology

- Spitz nevus is a spindle and epithelioid cell nevus.
- Histologic architecture may show fascicular growth.
- Cells can be large and plump with pink-blue cytoplasm.
- Fusiform cells may coexist with epithelioid cells.

Spitz nevus: Often an erythematous nodule



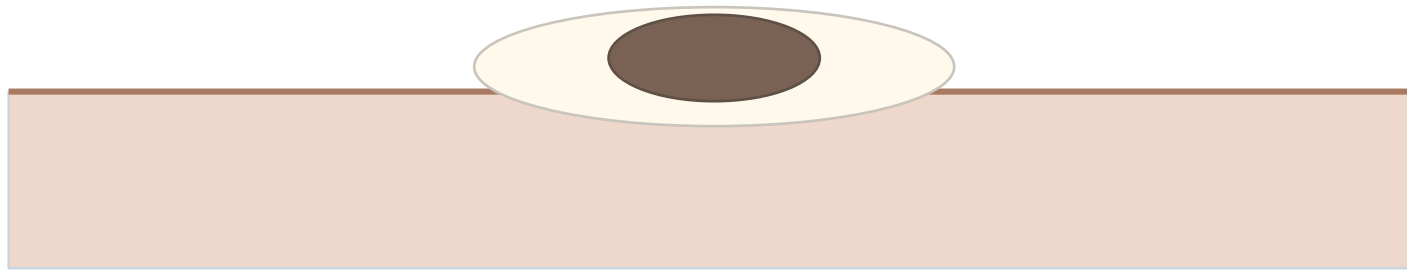
- Common in children.
- Frequently a red-pink nodule.
- Can resemble hemangioma clinically.

Schematic surface profile — not a clinical photograph

Halo nevus: A host immune response

- Nevus cells can be surrounded by a lymphocytic infiltrate.
- The host response targets nevus cells and adjacent normal melanocytes.
- Loss of surrounding pigment produces the characteristic halo phenotype.
- The central nevus cells may otherwise resemble ordinary nevi.

Halo nevus: Depigmentation around a central mole



- Central nevus.
- Pale surrounding zone.
- Lymphocyte-mediated response.

Schematic surface profile — not a clinical photograph

Nevus variants: Architecture and clinical clue

Variant	Distinctive histologic pattern	Practical clinical clue
Congenital	Deep periadnexal / neurovascular growth	Present at birth; Large lesions carry risk
Blue	Dendritic, pigmented cells; Dermal infiltration	Black-blue nodule
Spitz	Spindle / epithelioid cells; Fascicles	Childhood red-pink nodule
Halo	Lymphocytes around nevus cells	Depigmented surrounding halo

Clinical similarity does not equal same histology

Blue nevus

- Black-blue nodule.
- Dendritic pigmented cells.
- Diffuse nonnested dermal architecture.

Spitz nevus

- Red-pink nodule.
- Plump spindle / epithelioid cells.
- Fascicular architecture.

Dysplastic nevus: Related but distinct entity

- A dysplastic nevus is not identical to an ordinary acquired nevus.
- The adjacent Robbins section notes coalescent intraepidermal nests.
- Cytologic atypia can be present.
- Recognizing the distinction matters because dysplastic nevi mark melanoma risk.

Ordinary nevus versus dysplastic nevus

Ordinary acquired nevus

- Common symmetrical pattern.
- Bland uniform nevus nuclei.
- Maturation with dermal depth.

Dysplastic nevus

- Coalescent intraepidermal nests.
- Cytologic atypia.
- May indicate increased melanoma risk.

Risk marker versus direct precursor

- Most dysplastic nevi remain clinically stable.
- Some can be direct precursors of melanoma, but progression is uncommon.
- Multiple dysplastic nevi may indicate a heightened melanoma risk background.
- A risk marker does not imply every nevus becomes malignant.

How the ordinary nevus is distinguished from melanoma

- Orderly and well-circumscribed growth supports nevus architecture.
- Uniform nuclear appearance and sparse mitoses are reassuring findings.
- Progressive maturation with depth is a key benign pattern.
- Melanoma generally lacks such characteristic maturation.

Nevus–melanoma distinction: Integrated clues

Nevus-favoring

- Symmetry and uniform pigment.
- Maturing cells with depth.
- Small inconspicuous nucleoli.
- Minimal mitoses.

Features that warrant concern

- Irregular overall architecture.
- Failure of ordered maturation.
- Marked cytologic atypia.
- Proliferation incongruent with a banal nevus.

Diagnostic pitfall: Overinterpreting RAS or BRAF

- An activating pathway mutation is compatible with a benign nevus.
- The biologic context includes p16-mediated senescence.
- Mutation presence alone is not equivalent to melanoma diagnosis.
- Histopathologic pattern remains the central diagnostic evidence.

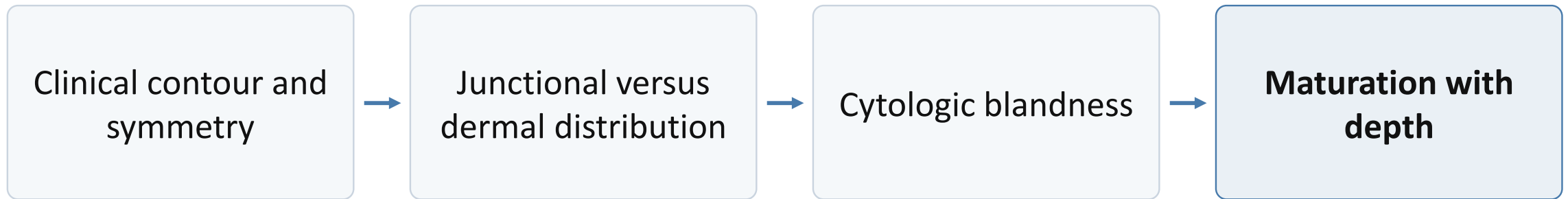
Diagnostic pitfall: Judging a nevus by color alone

- Blue nevi can be intensely dark but benign.
- Spitz nevi may be pink rather than brown.
- Halo nevi may lose surrounding pigmentation.
- Clinical color is insufficient to infer the underlying subtype.

Diagnostic pitfall: Treating all nevus types alike

- Ordinary acquired nevi are common and predominantly benign.
- Large congenital nevi have a different stated risk profile.
- Dysplastic nevi may mark an increased melanoma-risk background.
- Clinical history and subtype should shape interpretation.

A morphology-first reading sequence



Read the entire lesion: No single favorable feature replaces integrated assessment.

Case 1 — identify the architectural nevus

A small, symmetric, flat brown macule shows round melanocyte nests limited to the dermoepidermal junction.

- Junctional nevus
- Compound nevus
- Intradermal nevus

Case 2 — explain a raised benign mole

A dome-shaped mole contains junctional nests plus cords of melanocytes in the upper dermis.

- Junctional nevus
- Compound nevus
- Pure intradermal nevus

Case 3 — interpret deep spindle-shaped cells

A dermal nevus has progressively smaller, less pigmented cells; Its deepest cells are spindle-shaped in fascicles.

- Maturation and neurotization
- Evidence of a neural tumor
- Proof of melanoma

Case 4 — a red-pink lesion in a child

A child has a red-pink skin nodule. Histology shows large epithelioid and spindle-shaped nevus cells with fascicular growth.

- Spitz nevus
- Blue nevus
- Halo nevus

Case 5 — oncogenic mutation in a benign lesion

Molecular analysis of a bland melanocytic nevus identifies an activating BRAF alteration. Which conclusion is supported?

- The mutation can initiate nevus growth.
- The lesion must be melanoma.
- The lesion cannot undergo growth arrest.

Three anchors for accurate interpretation

Biology

- RAS/BRAF activation initiates growth.
- P16-associated senescence restrains growth.
- Mutations alone do not define melanoma.

Architecture

- Junctional nests first.
- Compound lesions contain dermal growth.
- Older lesions may be intradermal.

Maturation

- Deep cells become smaller.
- Pigment and tyrosinase decline.
- Neurotization may occur.

Key morphologic conclusions

- A nevus is a benign melanocytic neoplasm, not merely a pigmented macule.
- Junctional, compound, and intradermal patterns describe cell location.
- Nevus cells typically mature as they extend more deeply.
- Recognize distinct variants and the separate significance of dysplastic nevi.

Selected source and illustration status

Primary textbook

Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. 2026. Chapter 25: The Skin.
“Melanocytic Nevus,” printed p. 1031.

Parent-context material

Table 25.2 (representative nevus variants), adjacent Dysplastic Nevi section; Freckle / Lentigo neighboring text.

Visual disclosure

All tissue, cell, and clinical morphology drawings are original native PowerPoint schematics, not specimen photographs.